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FILE COVERS 1907 - 9 Sep 2003  VOL 139 ISS 11
FILE LAST UPDATED: 8 Sep 2003  (20030908/ED)

  This file contains CAS Registry Numbers for easy and accurate
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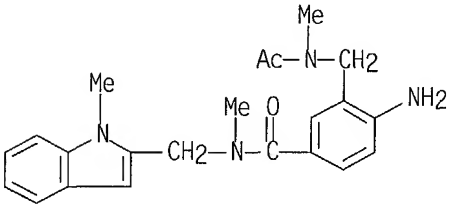
L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:737377 CAPLUS
DOCUMENT NUMBER: 138:280765
TITLE: Discovery of a novel and potent class of FabI-directed antibacterial agents
AUTHOR(S): Payne, David J.; Miller, William H.; Berry, Valerie; Brosky, John; Burgess, Walter J.; Chen, Emile; DeWolf, Walter E., Jr.; Fosberry, Andrew P.; Greenwood, Rebecca; Head, Martha S.; Heerding, Dirk A.; Janson, Cheryl A.; Jaworski, Deborah D.; Keller, Paul M.; Manley, Peter J.; Moore, Terrance D.; Newlander, Kenneth A.; Pearson, Stewart; Polizzi, Brian J.; Qiu, Xiayang; Rittenhouse, Stephen F.; Slater-Radosti, Courtney; Salyers, Kevin L.; Seefeld, Mark A.; Smyth, Martin G.; Takata, Dennis T.; Uzinskas, Irene N.; Vaidya, Kalindi; Wallis, Nicola G.; Winram, Scott B.; Yuan, Catherine C. K.; Huffman, William F.
CORPORATE SOURCE: Microbial, Musculoskeletal and Proliferative Diseases Center of Excellence in Drug Discovery, GlaxoSmithKline Pharmaceuticals, Collegeville, PA, 19426, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(10), 3118-3124
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:
Bacterial enoyl-acyl carrier protein (ACP) reductase (FabI) catalyzes the final step in each elongation cycle of bacterial fatty acid biosynthesis and is an attractive target for the development of new antibacterial agents. High-throughput screening of the Staphylococcus aureus FabI enzyme identified a novel, weak inhibitor with no detectable antibacterial activity against S. aureus. Iterative medicinal chem. and x-ray crystal structure-based design led to the identification of compd. 4 [(E)-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide], which is 350-fold more potent than the original lead compd. obtained by high-throughput screening in the FabI inhibition assay. Compd. 4 has exquisite antistaphylococci activity, achieving MICs at which 90% of isolates are inhibited more than 500 times lower than those of nine currently available antibiotics against a panel of multidrug-resistant strains of S. aureus and Staphylococcus epidermidis. Furthermore, compd. 4 exhibits excellent in vivo efficacy in an S. aureus infection model in rats. Biochem. and genetic approaches have confirmed that the mode of antibacterial action of compd. 4 and related compd. is via inhibition of FabI. Compd. 4 also exhibits weak FabK inhibitory activity, which may explain its antibacterial activity against Streptococcus pneumoniae and Enterococcus faecalis, which depend on FabK and both FabK and FabI, resp., for their enoyl-ACP reductase function. These results show that compd. 4 is representative of a new, totally synthetic series of antibacterial agents that has the potential to provide novel alternatives for the treatment of S. aureus infections that are resistant to our present armory of antibiotics.

IT **334999-42-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(discovery of a novel and potent class of FabI-directed antibacterial agents)

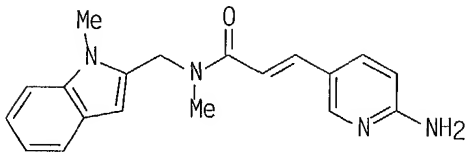
RN 334999-42-7 CAPLUS

CN Benzamide, 3-[(acetylmethylamino)methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:457916 CAPLUS
DOCUMENT NUMBER: 137:163327
TITLE: Discovery of Aminopyridine-Based Inhibitors of Bacterial Enoyl-ACP Reductase (FabI)
AUTHOR(S): Miller, William H.; Seefeld, Mark A.; Newlander, Kenneth A.; Uzinskas, Irene N.; Burgess, Walter J.; Heerding, Dirk A.; Yuan, Catherine C. K.; Head, Martha S.; Payne, David J.; Rittenhouse, Stephen F.; Moore, Terrance D.; Pearson, Stewart C.; Berry, Valerie; DeWolf, Walter E., Jr.; Keller, Paul M.; Polizzi, Brian J.; Qiu, Xiayang; Janson, Cheryl A.; Huffman, William F.
CORPORATE SOURCE: GlaxoSmithKline Pharmaceuticals, Collegeville, PA, 19426, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(15), 3246-3256
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GRAPHIC IMAGE:



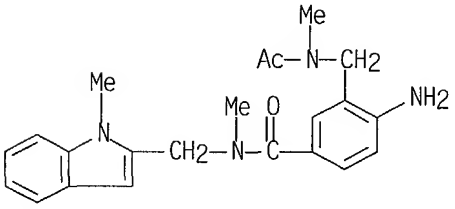
I

ABSTRACT:
Bacterial enoyl-ACP reductase (FabI) catalyzes the final step in each cycle of bacterial fatty acid biosynthesis and is an attractive target for the development of new antibacterial agents. Our efforts to identify potent, selective FabI inhibitors began with screening of the GlaxoSmithKline proprietary compd. collection, which identified several small-mol. inhibitors of Staphylococcus aureus FabI. Through a combination of iterative medicinal chem. and X-ray crystal structure based design, one of these leads was developed into the novel aminopyridine deriv. I, a low micromolar inhibitor of FabI from S. aureus (IC50 = 2.4 .mu.M) and Haemophilus influenzae (IC50 = 4.2 .mu.M). Compd. I has good in vitro antibacterial activity against several organisms, including S. aureus (MIC = 0.5 .mu.g/mL), and is effective in vivo in a S. aureus groin abscess infection model in rats. Through FabI overexpressor and macromol. synthesis studies, the mode of action of I has been confirmed to be inhibition of fatty acid biosynthesis via inhibition of FabI. Taken together, these results support FabI as a valid antibacterial target and demonstrate the potential of small-mol. FabI inhibitors for the treatment of bacterial infections.

IT **334999-42-7P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminopyridines as antibacterial enoyl ACP reductase inhibitors)

RN 334999-42-7 CAPLUS

CN Benzamide, 3-[(acetylmethylamino)methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:283787 CAPLUS
DOCUMENT NUMBER: 134:311104
TITLE: Preparation of N-(indolylmethyl) benzamides as Fab I inhibitors
INVENTOR(S): Miller, William H.; Newlander, Kenneth A.; Seefeld, Mark A.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001026654	A1	20010419	WO 2000-US27591	20001006
W: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1225895	A1	20020731	EP 2000-973420	20001006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003511415	T2	20030325	JP 2001-529444	20001006

PRIORITY APPLN. INFO.: US 1999-158529P P 19991008
WO 2000-US27591 W 20001006
OTHER SOURCE(S): MARPAT 134:311104
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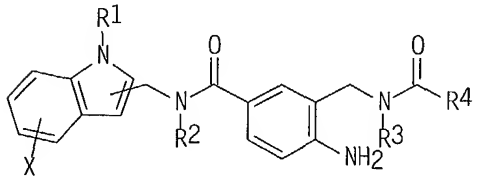

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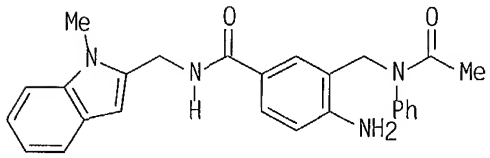
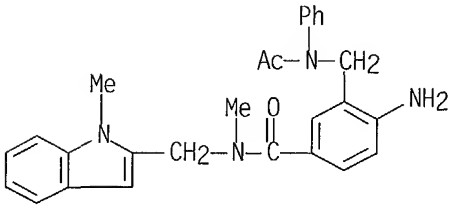


II

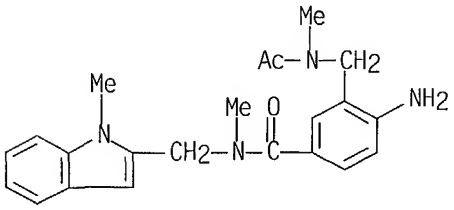
ABSTRACT:
The title compds. [I; R1 = alkyl; R2 = alkyl; R3 = alkyl, alkylAr, alkylHet; R4 = alkyl, Oalkyl, N(alkyl)2, etc.; X = H, alkyl, CN, etc.] which are Fab I inhibitors and are useful in the treatment bacterial infections, were prepd. and formulated. E.g., a multi-step synthesis of II was given. The compds. I showed IC50 of 0.15-4.0 .mu.M in E. coli FabI enzyme inhibition assay.

IT **334999-40-5P 334999-42-7P 334999-44-9P**
334999-46-1P 334999-49-4P 334999-50-7P
334999-52-9P 334999-54-1P 334999-56-3P
334999-58-5P 334999-59-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-(indolylmethyl) benzamides as Fab I inhibitors)

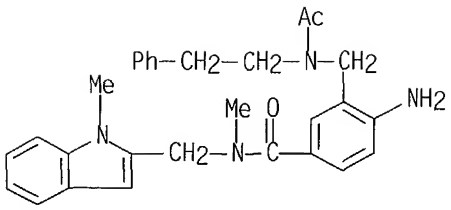
RN 334999-40-5 CAPLUS
CN Benzamide, 3-[(acetylphenylamino)methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



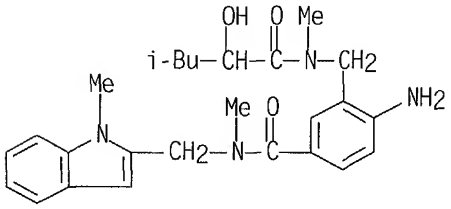
RN 334999-42-7 CAPLUS
CN Benzamide, 3-[(acetylmethylamino)methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



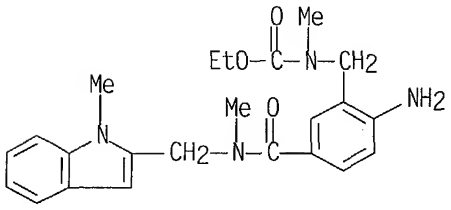
RN 334999-44-9 CAPLUS
CN Benzamide, 3-[[acetyl(2-phenylethyl)amino]methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



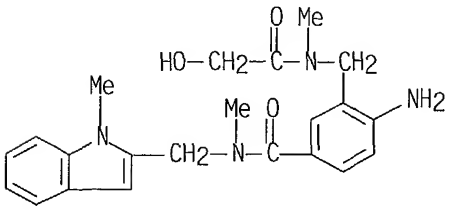
RN 334999-46-1 CAPLUS
CN Benzamide, 4-amino-3-[[(2-hydroxy-4-methyl-1-oxopentyl)methylamino]methyl]-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



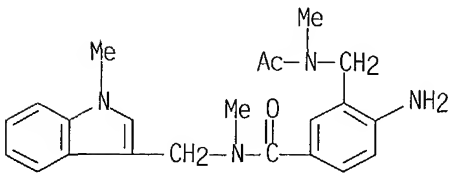
RN 334999-49-4 CAPLUS
CN Carbamic acid, [[2-amino-5-[[methyl[(1-methyl-1H-indol-2-yl)methyl]amino]carbonyl]phenyl]methyl]methyl-, ethyl ester (9CI) (CA INDEX NAME)



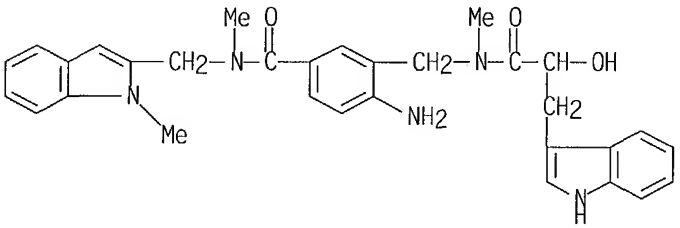
RN 334999-50-7 CAPLUS
CN Benzamide, 4-amino-3-[[(hydroxyacetyl)methylamino]methyl]-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



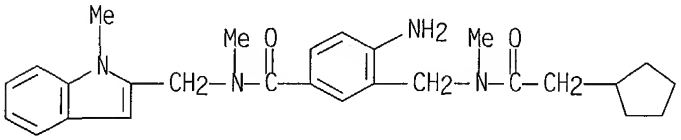
RN 334999-52-9 CAPLUS
CN Benzamide, 3-[(acetylmethylamino)methyl]-4-amino-N-methyl-N-[(1-methyl-1H-indol-3-yl)methyl]- (9CI) (CA INDEX NAME)



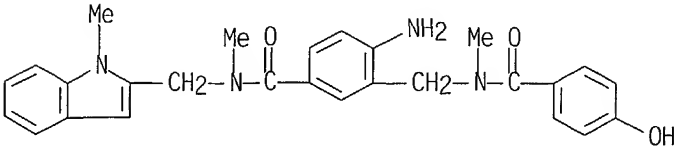
RN 334999-54-1 CAPLUS
CN 1H-Indole-3-propanamide, N-[[2-amino-5-[[methyl[(1-methyl-1H-indol-2-yl)methyl]amino]carbonyl]phenyl]methyl]-.alpha.-hydroxy-N-methyl- (9CI) (CA INDEX NAME)



RN 334999-56-3 CAPLUS
CN Benzamide, 4-amino-3-[[(cyclopentylacetyl)methylamino]methyl]-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)

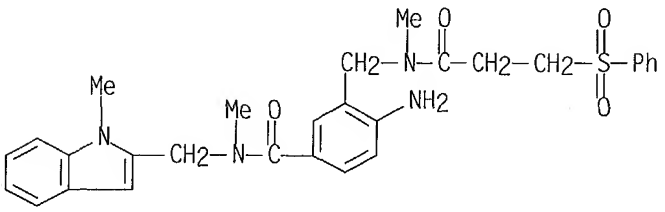


RN 334999-58-5 CAPLUS
CN Benzamide, 4-amino-3-[[(4-hydroxybenzoyl)methylamino]methyl]-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]- (9CI) (CA INDEX NAME)



RN 334999-59-6 CAPLUS

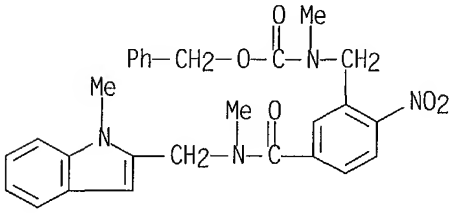
CN Benzamide, 4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]-3-[[methyl[1-oxo-3-(phenylsulfonyl)propyl]amino]methyl]- (9CI) (CA INDEX NAME)



IT **334999-84-7P 334999-88-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-(indolylmethyl) benzamides as Fab I inhibitors)

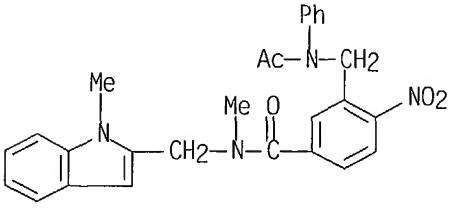
RN 334999-84-7 CAPLUS

CN Carbamic acid, methyl[[5-[[methyl[(1-methyl-1H-indol-2-yl)methyl]amino]carbonyl]-2-nitrophenyl]methyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 334999-88-1 CAPLUS

CN Benzamide, 3-[(acetylphenylamino)methyl]-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]-4-nitro- (9CI) (CA INDEX NAME)



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FILE LAST UPDATED:  01 May 1997 (19970501/UP)

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  display formats.

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  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

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